Claims

1. An isolated multiply acetylated protein HMGB1; or a variant or fragment thereof, or a polynucleotide encoding therefor.

2. An isolated acetylated HMGB1; or a variant or fragment thereof, or a polynucleotide encoding therefor, with the proviso that lysines 2 and 11 are not acetylated

3. An isolated acetylated protein HMGB1 derivable from a myeloid cell; or a variant or fragment thereof, or a polynucleotide encoding therefor.

4. A protein according to any preceding claim in which at least one nuclear localization signal is acetylated.

5. A protein according to any preceding claim in which with reference to Figure 2C at least one or more of lysines 27, 28, 29,179, 181, 182, 183 or 184 are acetylated.

6. A protein according to any preceding claim having the acetylation pattern of Figure 2C.

7. An expression vector comprising the polynucleotide of any preceding claim.

8. A host cell comprising the expression vector of claim 7.

9. A pharmaceutical composition comprising an acetylated protein HMGB1 according to any preceding claim and a pharmaceutically acceptable carrier, excipient or diluent.

10. A method of identifying an agent that is a modulator of acetylated protein HMGB1 or of the acetylation of protein HMGB1; or a variant or fragment thereof, or a polynucleotide encoding therefor, comprising the steps of:

determining acetylated protein HMGB1 activity in the presence and absence of said agent;

comparing the activities observed in step (a); and

identifying said agent as a modulator by the observed differences in acetylated protein HMGB1 activity in the presence and absence of said compound.

11. A method according to claim 10 wherein the activity is observed via modulation of the acetylation of protein HMGB1.

12. A modulator of an isolated acetylated protein HMGB1 or of the acetylation of protein HMGB1; or a variant or fragment thereof, or a polynucleotide encoding therefor.

13. A modulator according to claim 12 identifiable using the method of claim 10 or 11.

14. A modulator according to claim 12 or 13 which modulates a pathway downstream of ras and/or Rac/CDC42, modulates active export form the nucleus, modulates the activation of a myeloid cell, modulates the binding of LPS to a cell, modulates the binding of an inflammatory cytokine to a cell, modulates a MAP kinase pathway, modulates the NF-κB pathway, modulates LPC signalling, modulates an histone acetyl transferase enzyme or modulates deactylase inhibitor.

15. A modulator according to claim 14 wherein the inflammatory cytokine is IL-1β, TNF-α, LPS or HMGB1.

16. A modulator according to claim 14 wherein the pathway downstream of Rac/CDDC42 is the ERK, Jnk or p38 pathway.

17. A modulator according to claim 14 wherein export from the nucleus may be modulated by using an modulator of CRM1exportin binding to HMGB1, a modulator of phosphorylation of ERK, or a modulator of a histone acetyl transferase (HAT) enzyme.

18. A modulator according to claim 17 wherein the HAT enzyme is pCAF, CBP or p300.

19. A modulator according to any one of claims 12 or 18 in the form of an inhibitor of the acetylated protein HMGB1 or of the acetylation of protein HMGB1; or a variant or fragment thereof, or a polynucleotide encoding therefor.

20. A modulator according to claim 19 wherein the inhibitor is an antibody, an antisense sequence or an acetylated protein HMGB1 receptor antagonist.

21. A modulator according to claim 19 wherein the inhibitor of CRM1exportin binding to HMGB1 is leptomycin B or a functional mimetic thereof.

22. A modulator according to claim 19 wherein the modulator of phosphorylation of ERK is U0126 or a functional mimetic thereof.

23. A modulator according to any one of claims 12 to 18 in the form of an agonist of the acetylated protein HMGB1 or a variant or fragment thereof, or a polynucleotide encoding therefor, or of the acetylation of protein HMGB1 or a variant or fragment thereof.

24. A polynucleotide encoding the modulator of any one of claims 12 to 23.

25. An expression vector comprising the polynucleotide of claim 24.

26. A host cell comprising the expression vector of claim 25.

27. A pharmaceutical composition comprising a modulator according to any one of claims 12 to 23 and a pharmaceutically acceptable carrier, excipient or diluent.

28. A pharmaceutical composition according to claim 27 further comprising the protein HMGB1; or a variant or fragment thereof, or a polynucleotide encoding therefor, or a modulator of the protein HMGB1 or a variant or fragment thereof, or a polynucleotide encoding therefor.

29. A pharmaceutical composition according to claim 28 wherein the modulator of HMGB1 is an upregulator of the protein HMGB1.

30. A pharmaceutical composition according to claim 28 or 29, in the form of a vaccine.

31. A pharmaceutical composition according to any one of claims 28 to 30 further comprising an antigen.

32. A pharmaceutical composition according to any one of claims 28 to 31 further comprising an APC.

33. A method for treating a condition associated with activation of the inflammatory cytokine cascade comprising administering an effective amount of an inhibitor according to any one of claims 12 to 22.

34. The method according to claim 33 wherein the condition is sepsis or a related condition.

35. The method according to claim 33 or 34 further comprising administering a second agent in combination with the modulator, wherein the second agent is an inhibitor of an early sepsis mediator.

36. The method of claim 35 wherein the second agent is an inhibitor of a cytokine selected from TNF, IL-1α, IL-1β, MIF and IL-6.

37. The method of claim 35 wherein the second agent is an antibody to TNF or an IL-1 receptor antagonist (IL-1ra).

38. A method of monitoring the severity and/or predicting the clinical course of sepsis and related conditions comprising measuring the concentration of acetylated protein HMGB1 in a sample, and comparing that concentration to a standard for acetylated protein HMGB1 representative of a normal concentration range of acetylated protein HMGB1 in a like sample, whereby higher levels of acetylated protein HMGB1 are indicative of severe conditions and/or toxic reactions.

39. A method of diagnosing and/or predicting the course of conditions associated with the activation of the inflammatory cascade comprising measuring the concentration of acetylated protein HMGB1 in a sample, and comparing that concentration to a standard for acetylated protein HMGB1 representative of a normal concentration range of acetylated protein HMGB1 in a like sample, whereby higher levels of acetylated protein HMGB1 are indicative of such conditions and/or severe conditions.

40. The method of claim 38 or 39 wherein the sample is a serum sample.

41. A method for effecting weight loss or treating obesity comprising administering an effective amount of acetylated protein HMGB1; or a fragment or variant thereof, or a polynucleotide encoding therefor, or a modulator according to any one of claims 12 to 22.

42. Use of a modulator of any one of claims 12 to 23 for administering to a patient undergoing therapy with the protein HMGB1; or a fragment or variant thereof, or a polynucleotide encoding therefor; an agonist of the protein HMGB1 or a fragment or

variant thereof; or an antagonist of the protein HMGB1 or a fragment or variant thereof.

43. A method for stimulating an immune response comprising administering the protein HMGB1; or a variant or fragment thereof, or a polynucleotide encoding therefor, and an inhibitor according to any one of claims 12 to 22.

44. A method for the prevention of treatment of cancer or a bacterial or viral infection comprising administering the protein HMGB1; or a variant or fragment thereof, or a polynucleotide encoding therefor, and an inhibitor according to any one of claims 12 to 22.

45. A method for producing an activated APC comprising exposing the APC to the protein HMGB1; or a variant or fragment thereof, or a polynucleotide encoding therefor, and an inhibitor according to any one of claims 12 to 22.

46. A method according to claim 45 wherein the APC is exposed *in vitro*.

47. A method according to claim 45 or 46 wherein the APC is also exposed to an antigen.

48. A method according to claim 47 wherein the APC is exposed to the antigen *in vivo*.

49. A method according to any one of claims 43 to 48 wherein the inhibitor is administered *in vivo*.

50. A method according to any one of claims 45 to 49 wherein the APC and/or antigen are also exposed to a T cell.

51. A method according to claim 50 wherein the APC and/or antigen is exposed to the T cell *in vivo*.

52. A method according to any one of claims 47 to 51 wherein the antigen is a tumor, bacterial or viral antigen.

53. A method according to any one of claims 43 to 52 wherein the protein HMGB1 is in the form of a vaccine.

54. A method to induce stem cell migration and/or proliferation comprising the step of exposing such cells to HMGB1 and an inhibitor of acetylated HMGB1 according to any one of claims 12 to 22..

55. A method for the treatment of tissue repair and/or regeneration comprising the step of exposing such cells to HMGB1 and an inhibitor of acetylated HMGB1 according to any one of claims 12 to 22.